RESEARCH ARTICLE

Children show hemispheric differences in the basic auditory response properties

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Abstract

Auditory cortex in each hemisphere shows preference to sounds from the opposite hemifield in the auditory space. Besides this contralateral dominance, the auditory cortex shows functional and structural lateralization, presumably influencing the features of subsequent auditory processing. Children have been shown to differ from adults in the hemispheric balance of activation in higher-order auditory based tasks. We studied, first, whether the contralateral dominance can be detected in 7- to 8-year-old children and, second, whether the response properties of auditory cortex in children differ between hemispheres. Magnetoencephalography (MEG) responses to simple tones revealed adult-like contralateral preference that was, however, extended in time in children. Moreover, we found stronger emphasis towards mature response properties in the right than left hemisphere, pointing to faster maturation of the right-hemisphere auditory cortex. The activation strength of the child-typical prolonged response was significantly decreased with age, within the narrow age-range of the studied child population. Our results demonstrate that although the spatial sensitivity to the opposite hemifield has emerged by 7 years of age, the population-level neurophysiological response shows salient immature features, manifested particularly in the left hemisphere. The observed functional differences between hemispheres may influence higher-level processing stages, for example, in language function.

KEYWORDS

cortical maturation, development, electromagnetic brain imaging, N100m, N250m

1 | INTRODUCTION

Brain development, including that of the auditory pathway, is reflected in structural changes throughout childhood (e.g., Shaw et al., 2008). Children and adults show clear differences also in the temporal pattern of neurophysiological response as recorded with EEG and MEG (Kotecha et al., 2009; Ponton, Eggermont, Khosla, Kwong, & Don, 2002; Sussman, Steinschneider, Gumenyuk, Grushko, & Lawson, 2008). Although the importance of hemispheric specialization in auditory information processing has been established in adults (Boemio, Fromm, Brau, & Poeppel, 2005) and abnormalities in hemispheric balance have been suggested to underlie neurodevelopmental disorders (Johnson et al., 2013), the hemisphere-specific response pattern in children is surprisingly poorly understood. Interestingly, a recent MEG study indicated different lateralization of functions in 7-year-old children as compared with adults in auditory language processing (Nora

et al., 2017). However, a review on fMRI studies describes minor changes in language lateralization after the age of 6 years (Weiss-Croft & Baldeweg, 2015). For a better understanding of maturational changes in the role of the two hemispheres in processing auditory language, and auditory information in general, the basic auditory response properties in the two hemispheres in children, as compared with adults, must be established. Indeed, although age-specific differences in the structural (Toga, Thompson, & Sowell, 2006) and temporal (Wunderlich & Cone-Wesson, 2006) domains are described in the literature, a detailed understanding of the neural processes specific to the developing brain is lacking. In order to understand the mechanisms that relate to typical and deviant developmental trajectories, we need to approach the detailed spatiotemporal properties of the response pattern.

Auditory cortices in the two hemispheres receive input from both ears. However, input from the opposite spatial hemifield is

emphasized (Rosenzweig, 1951), reflected as stronger and earlier neural responses to sounds from the contralateral versus ipsilateral ear (Mäkelä et al., 1993; Pantev, Ross, Berg, Elbert, & Rockstroh, 1998; Salmelin et al., 1999). Neurophysiological responses measured using MEG in adults further show generally stronger responses in the right than in the left hemisphere, independent of the stimulated ear (Salmelin et al., 1999). Although the contralateral dominance in the auditory domain has been well established in adults, very little is known about its development in children. In this study, we aimed to clarify the auditory processing patterns in children, evoked by contralateral and ipsilateral stimulation, separately in each hemisphere.

One of the main consequences of postnatal cortical maturation—that includes myelination and strengthening of connections—is increased processing speed and temporal acuity (Dockstader, Gaetz, Rockel, & Mabbott, 2012). Characterization of the differences between mature and immature auditory processing must thus include information about the timing of neural processing. Ideally, this information would be extracted separately for the left and right auditory cortices, with their distinct spatial sensitivity and functional properties. Recording of the electric (EEG) or magnetic fields (MEG) from outside the skull provides a measure of neuronal activity with millisecond accuracy (Hari & Salmelin, 2012). The magnetic field distribution, in particular, can be readily decomposed to the underlying sources of neural current, thus enabling estimation and comparison of spatially tagged time courses of activation. MEG thus allows reliable comparison of activation in the left- and right-hemisphere auditory cortices (Mäkelä et al., 1993; Salmelin et al., 1999).

The time-course of transient synchronous neural activations is reflected as subsequent peaks in the averaged MEG or EEG response. The auditory brain stem responses (ABRs) are fairly stable across individuals and reflect the developmental stage of the subcortical auditory pathway (Hornickel & Kraus, 2013; Kraus & McGee, 1992; Starr & Amlie, 1981). Middle-latency responses (MLR) and late auditory evoked potentials/fields (AEP/F) with mainly cortical origin are more variable in latency. Nevertheless, the systematic changes in the cortical AEF morphology over the course of the first decade of life (and beyond; Ponton et al., 2002; Wunderlich & Cone-Wesson, 2006) are likely to carry information about the maturational state of the cortical auditory system (Eggermont, 1988; Parviainen, Helenius, Poskiparta, Niemi, & Salmelin, 2011), with potential relevance for individual differences in behavioral skills.

The cortical auditory response in adults, evoked by passive presentation of simple sounds, consists of a sequence of transient peaks from about 20 ms onwards. These responses localize to primary (20–50 ms) and nonprimary (~100 ms) auditory areas (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994; Mäkelä, Hämäläinen, Hari, & McEvoy, 1994; Parviainen, Helenius, & Salmelin, 2005). Based on previous EEG findings, the cortically evoked responses in young children are typically extended in time, first showing a positive deflection at 100 ms, followed by a longer-lasting negative deflection between 100 and 300 ms (Hamalainen, Ortiz-Mantilla, Benasich, 2011). The major age-related changes are an overall decrease in latency and emergence of early, transient components (Ponton et al., 2002; Takeshita et al., 2002).

It is not straightforward to draw general conclusions on the maturation of neural processes based on measures collected noninvasively from outside the skull, as the possible changes in the underlying neural generators are not known. Moreover, the reported effects depend, for example, on the choice of stimuli and their presentation rate (Orekhova et al., 2013; Rojas, Walker, Sheeder, Teale, & Reite, 1998; Sussman et al., 2008). Nonetheless, in contrast to the short-lived auditory activation in adults at around 100 ms, the most prominent response type systematically reported in children is a long-lasting activation that reaches the maximum at around 250 ms. This response type decreases in amplitude with age (Johnstone, Barry, Anderson, & Coyle, 1996) while the transient adult-like 100-ms response increases in amplitude and decreases in latency (Cunningham, Nicol, Zecker, & Kraus, 2000; Takeshita et al., 2002). These changes are likely to reflect structural and functional development of the underlying neuronal networks (Eggermont & Ponton, 2002).

In our earlier study of 7- to 8-year-old children (Parviainen et al., 2011) we described the pattern of auditory activation at the level of cortical sources and estimated the location and direction of current flow underlying the neural responses at ~100 ms and ~250 ms. At 100 ms most of the child subjects showed a current source parallel to the adult response at ~50 ms (P50m; with superior orientation of current flow), here referred to as P100m. At 250 ms all child subjects showed a current source with direction opposite to that of the P100m, thus parallel to the adult response at ~100 ms (N100m; with inferior orientation of current flow), here referred to as N250m. A few children showed an adult-like N100m activation already at ~100 ms.

While in adults the general response pattern for simple auditory stimuli is spatially and temporally fairly symmetric (Mäkelä et al., 1993), hemispheric differences have been indicated in children in the AEF source structure (Parviainen et al., 2011), and in the rate of change of the AEF peak latencies across development (Kotecha et al., 2009). Interestingly, MRI studies of early brain development reported differences between hemispheres in the emergence of sulcal patterns (Dubois et al., 2009). However, very few functional studies in children focused on hemispheric differences and, moreover, examined the effects of the stimulated ear on the auditory cortical activation in the same study. Responses to binaurally presented sounds are mixtures of inputs from both ears and would thus not reveal possible effects of contra- versus ipsilateral stimulation. Studies using monaural stimulation have not typically examined the two hemispheres separately (Takeshita et al., 2002; Tonnquist-Uhlen, Borg, & Spens, 1995) or have stimulated only one ear, either left or right (Parviainen et al., 2011; Ponton et al., 2002). One earlier study using MEG (Orekhova et al., 2013) demonstrated differential pattern of activation for contra- versus ipsilateral versus binaural clicks, but the large age range of children (8–15 years) precludes from making age-specific conclusions.

It is thus not known whether the contra- versus ipsilateral auditory responses in the left and right hemisphere demonstrate similar effects in early childhood as has been described in adults (Mäkelä et al., 1993). Moreover, the possible hemispheric difference reflecting maturation of the auditory system in children needs to be systematically examined by controlling the influence of the stimulated ear. Here, we studied the fundamental response properties of the auditory cortex in children. First, we examined the emergence of contralateral

dominance in the left and right hemispheres. Second, we compared the response properties in the two hemispheres. For a reliable comparison of age-groups we compared both temporal and spatial characteristics of activation by utilizing MEG which has proven highly suitable for studying auditory functions with high spatial and temporal resolution. We performed source analysis sensitive to the direction of the source current, as it provides an important parameter for neurophysiological interpretation of the results. We expected to demonstrate a stronger emphasis on neural responses at ∼250 ms in children than in adults, but with comparable current orientation across age groups. Contralateral preference was assumed to be evident in children at this age in both hemispheres, but in general, we expected to find more mature response characteristics in the right hemisphere.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

All our subjects were volunteers. Informed consent was obtained from all adults. As regards the underaged participants, an informed consent was obtained from both the subject and their parents, in agreement with a prior approval of the Helsinki and Uusimaa Ethics Committee.

2.2 | Subjects

The subjects were 19 children (10 girls and 9 boys, 7.2–8.0 years) and 10 adults (5 females, 5 males, 23–39 years). All subjects were native, right-handed Finnish speakers, with no history of neurological abnormalities, auditory processing disorders or developmental language impairments.

2.3 | Stimuli

The stimuli were 1-kHz sine-wave tones, 50 ms in duration (10 ms fade-in and fade-out periods). They were presented alternatingly to the left and right ear at 60 dB above the subjective hearing level. The interstimulus interval (ISI) varied between 0.8 and 1.2 s. The individual hearing level was estimated prior to the measurement by using the stimulus sounds, delivered separately to each ear.

2.4 | MEG recordings

Stimuli were controlled with the Presentation program (Neurobehavioral Systems Inc., San Fransisco, CA) running on a PC. MEG signals were recorded using a helmet-shaped 306-channel whole-head system (Vectorview™, Elekta Neuromag Oy, Helsinki, Finland) with two orthogonally oriented planar gradiometers and one magnetometer in 102 locations.

During the measurement, subjects were seated, with the head covered by the MEG helmet, watching silent cartoons and not paying attention to the stimuli. The MEG signals were bandpass filtered at 0.03–200 Hz, sampled at 600 Hz, and averaged off-line across trials in the time-window from −0.2 s to 1 s relative to the stimulus onset. Horizontal and vertical eye movements were monitored (electrooculogram, EOG) and epochs contaminated by blinks or saccades were excluded from the average. In children, the heart is located fairly close to the measurement helmet, resulting in potential artifact signals from the heartbeat. In order to minimize the effects of such disturbances, the MEG signals were additionally off-line averaged with respect to the heart signal that was clearly detectable in the raw MEG signal along the rim of the helmet. Principal component analysis (PCA) was performed on this average and the magnetic field component produced by the heartbeat was removed from the data (Uusitalo & Ilmoniemi, 1997). In addition, the data was manually inspected to exclude epochs contaminated by notable artifacts. On average 102 (±4)/105 (±4) (mean ± SD) artifact-free epochs per subject for left/right sounds were gathered in adults and 92 (±13)/93 (±13) artifact-free epochs per subject for left/right sounds in children.

The position of the subject's head within the MEG helmet was defined with the help of four head position indicator (HPI) coils attached to the subject's head. To enable spatial alignment of the functional MEG data with structural MR brain images (when available), the locations of the HPI coils, were defined with respect to three anatomical landmarks (nasion, preauricular reference points) and the measurement helmet. In the off-line analysis of the data, a spherical estimation was used to describe the conductivity profile of the brain. Structural MR images were available for the adults. For the healthy children in the present study, an average sphere model of a small number of children (6–11 years) previously studied in our laboratory was used.

2.5 | Data analysis

The MEG signals were first low-pass filtered at 40 Hz. The signals detected with MEG are generated by synchronous activation in the apical dendrites of a large population of pyramidal cells. To estimate brain-level time courses of activation, equivalent current dipole (ECD) modeling was applied to the data of each individual subject (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The ECDs represent the average (summed) distribution of electric current in the cortex, giving an estimate of the location, strength and direction of local current flow. We especially sought to estimate the direction of the current flow across the activation time-course, as it allows to examine in detail the underlying electrophysiological processes in the two age groups.

The magnetic field patterns were visually inspected to identify local dipolar fields, indicative of separable, active neuron populations. Sensors covering each of these patterns were used to estimate the corresponding ECDs, for each subject. The peaks in the sensor-level evoked responses typically corresponded to salient dipolar field patterns (cf. Figure 2). During the 1-s interval after stimulus onset, the MEG sensor waveforms evidenced, in adults, only one clear peak of activation (∼100 ms) and, in children, two windows of activation (∼100 ms and 200–400 ms). In general, the activation prior to 200 ms reflected transient responses, whereas activation after 200 ms was longer-lasting, in both age groups.

In all adult subjects, one ECD in each temporal lobe sufficed to account well for the measured data across all MEG sensors and during the entire epoch (−200 ms ... +1,000 ms). In children, 1–3 ECDs in each hemisphere were needed to explain the measured signal. The set of identified ECDs were used simultaneously as a multi-dipole model

for the data of an individual subject. The locations and orientations of the ECDs were kept fixed while their amplitudes were allowed to vary to best explain the signals recorded by all sensors over the entire averaging interval. At individual level, the same individual set of ECDs accounted for the activation patterns evoked by both ipsilateral and contralateral stimulation.

Within each age-group, the sources with similar spatial characteristics (location and current direction) and general timing across subjects were considered to reflect comparable functional processes. Consistently with the main peaks in sensor-level waveform (and featuring the well-documented components of auditory evoked responses) the time-windows of interest were, in adults: 40–90 ms (corresponding to the P50m response), 90–150 ms (N100m response), 130–400 (P2m response), and 160–400 (N2m response); and in children, <200 ms (P100m/N100m response) and >200 ms (N250m response).[1] Although the N100m time-window was the only one showing stronger peak in the present study, the time-windows of all these major AER components were included in adults. We collected the maximum amplitude, and the time of reaching this value (maximum latency) from each individual in these time-windows. For the sustained N250m activation, the time points at which the waveform reached half of the maximum amplitude in the ascending and descending slopes were additionally determined, and the mean amplitude and duration measured between these time points.

2.6 | Statistical analysis

A repeated-measures mixed-model ANOVA with stimulation site (left ear, right ear) and hemisphere (left, right) was used to evaluate systematic effects in strength and timing of contralateral and ipsilateral auditory activation. Separate ANOVAs were conducted for adults and children, as the activation types were not unequivocally comparable across age groups (see below). Time-window (activation type) was included in the first omnibus ANOVA with four separate time-windows in adults (P50m, N100m, P2m, and N2m) and two separate time-windows in children (P100m/N100m and N250m). Further, when significant interactions were detected, separate ANOVAs for each time-window were conducted.

For a meaningful comparison between adults and children, one should compare corresponding activation types in the two age groups. Because the cortical responses of adults and children have a widely different appearance, it is uncertain whether the comparison is done most correctly by focusing on the same time windows in adults and children (i.e., activation at ∼100 ms) or on activation with similar spatial characteristics, such as direction of current flow. These two options reflect different underlying assumptions of the maturational changes in the cortex, that is, whether the maturational changes appear as changes in the spatial organization of current flow or as changes in timing. As known properties of anatomical maturation support the latter interpretation (cf. Section 1), we focused on responses with similar underlying orientation of neural current flow. The

difference between groups was tested using independent samples *t*-test, Bonferroni corrected for the number of comparisons.

3 | RESULTS

3.1 | Comparison of activation in adults versus children at MEG sensor level

Figure 1 shows the measured neuromagnetic responses, averaged over each age group (children vs. adults overlaid) in the planar gradiometer sensors for both left and right ear sounds. The contra- and ipsilateral auditory stimuli evoke responses roughly at the same time (thick vs. thin line) but the timing of the major activation peaks differs markedly between the age groups. The main activation in adults is evoked at around 100 ms (N100m) after sound onset in both the left and right hemisphere. In children, strong activation emerges later, after 200 ms. At the time of N100m response in adults the waveform
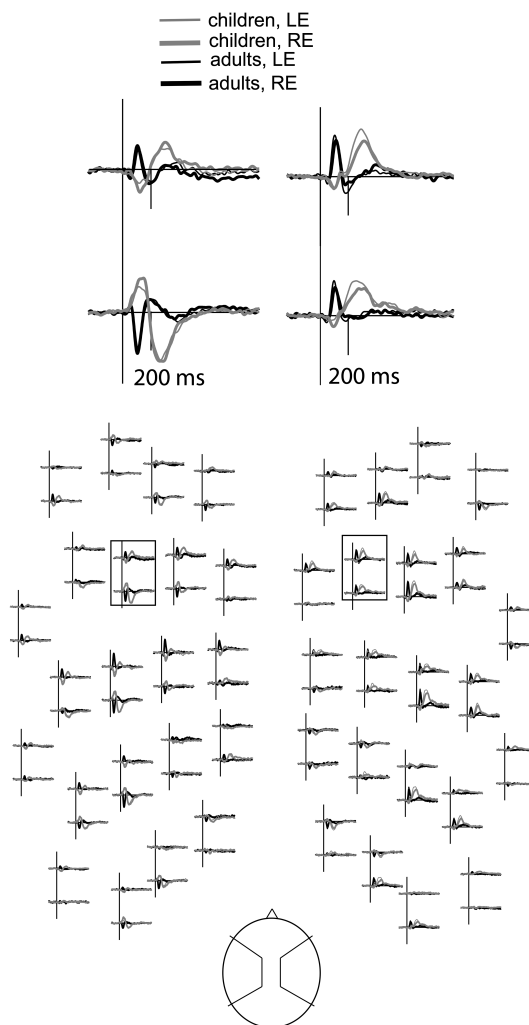

FIGURE 1 Distribution of MEG signals in the individual sensors of the measurement helmet. Auditory responses evoked by the left (thin line) and right (thick line) ear sounds in children (gray lines) and in adults (black lines) are overlaid. Two selected sensors (rectangles) are shown enlarged, illustrating the difference between age groups in timing of major activation peaks

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[1] P/N refer to the positive/negative polarity of the response in EEG nomenclature, m refers to the magnetic counterpart of these responses
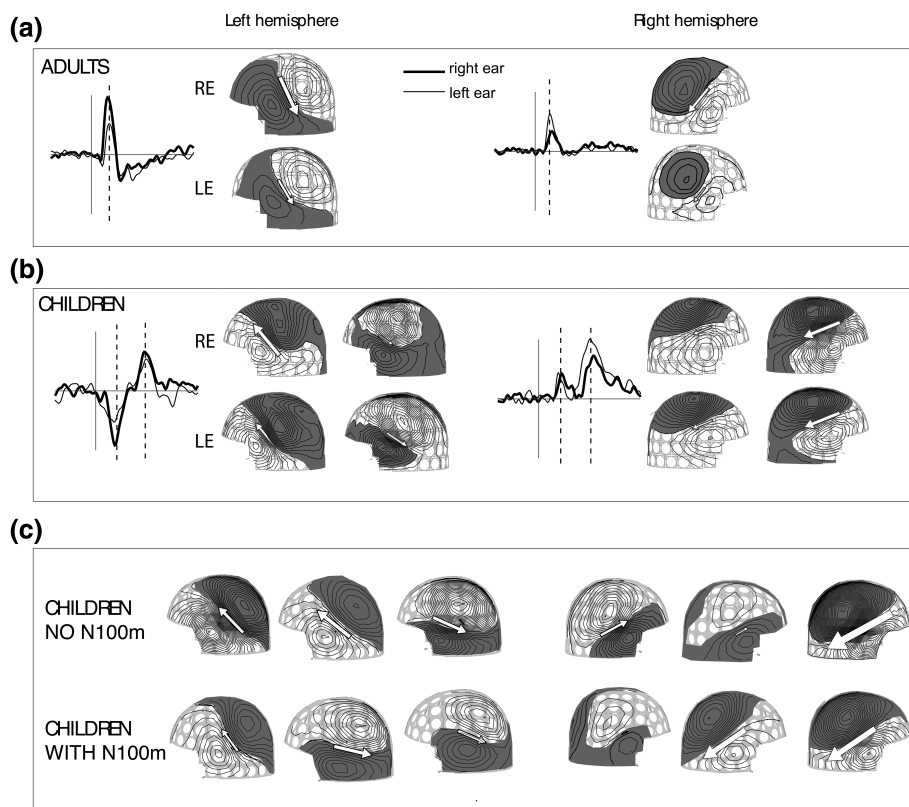
FIGURE 2 Source analysis. Signals recorded by selected MEG sensor and the magnetic field patterns in the left and right hemisphere in one adult subject (a) and one child subject (b) at the time of the peak (dashed line). In adults one local maximum (at ~100 ms, N100m) and in children, two local maxima (at ~100 ms, N100m/P100m; and at ~250, N250m) in activation emerged in both hemispheres. In children, the typical pattern reflected upward P100m—downward N250m responses, and some subjects demonstrated also transient downward N100m source, illustrated in grand-averaged field patterns separately for those who had the N100m source and those who did not have the N100m source (c)

in children shows a peak with the polarity opposite to that of the adult response, particularly clearly in the left hemisphere.

3.2 | Sequence of activation in adults versus children at the level of neural sources

The source model in all subjects indicated activation of the supratemporal auditory cortex of the left and right hemisphere. Figure 2 shows, in a helmet array, the location and direction of the source configuration in a typical adult (Figure 2a) and child (Figure 2b) subject. In adults, the spatial distribution of activation was comparable across all subjects. The strong and only clear response at 100 ms showed the characteristic N100m current distribution, both in the left and right hemispheres. The pattern was comparable for contra- and ipsilateral stimulation. In children, the activation was more extended in time and reflected more variable source configurations across individuals.

For further characterization of the distribution and time-course of activation in children, we divided the individually identified sources of neural current (ECDs) to those with maximum activation prior to 200 ms and those with maximum activation after 200 ms. The transient responses with maximum at <200 ms reflected either "upward" (superior) or "downward" (inferior) direction of the current flow, roughly at the same location. The responses at >200 ms reflected typically longer-lasting downwards/inferiorly directed current. Three distinct categories of activation thus emerged: (a) early transient

activation reflecting *upwards/superiorly* directed ECDs (P100m, in 19/19 individuals in the left hemisphere, and in 12/19 individuals in the right hemisphere), (b) early transient activation reflecting *downwards/inferiorly* directed ECDs (N100m, 4/19 in the left hemisphere, 9/19 in the right hemisphere), and (c) late longer-lasting activation reflecting *downwards/inferiorly* directed ECDs (N250m, 16/19 in the left hemisphere, 18/19 in the right hemisphere).

For the early (<200 ms) time-window there was thus interindividual variability in the dominant direction of the current flow. Figure 2c shows two separate grand averages for children, one computed across those children who did not manifest the N100m type current flow and one for across those children who showed this field pattern; summing across these two groups would not be as informative because the opposite field patterns of N100m and P100m would cancel each other out. The source configuration is illustrated at the time of main activation peaks, reflecting the transient P100m source in the time window 0–100 ms in both subject groups, a transient N100m or P100m source in the time window 100–200 ms, and a longer-lasting N250m source in the time window 200–300 ms again for both subject groups.

Figure 3 illustrates the timing of the different responses (latency of the maximum amplitude) in individual subjects. Comparison of the peak latencies between adults and children shows that the transient P100m response in children roughly coincides with the transient N100m response in adults (around 100 ms). The longer-lasting
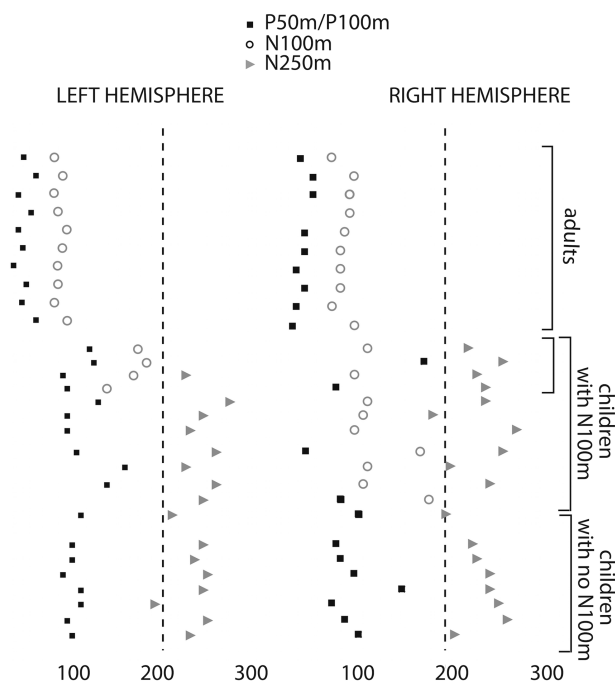
FIGURE 3 The distribution of peak latencies (maximum amplitude) for the three response types in individual subjects. P100m/P50m (black squares), N100m (empty circles) and N250 m (gray triangles) are depicted in individual adults (above) and children (below)

N250 m response in children appears clearly later, and in this time-window no significant peaks appear in adults. The transient N100m response in children is not present in all individuals, but some of the children showed both P100m and N100m type responses. In the left hemisphere, the N100m type response in children occurs between 100 ms and 250 ms, but in the right hemisphere it peaks earlier, with comparable latencies to the adult N100m response. Notably, all the adults show a transient N100m response in both hemispheres, but in children the number of subjects with this identifiable response type is larger in the right than in the left hemisphere.

Figure 4 shows the grand average waveform of these different cortical response types in children (P100m, N100m, and N250m) and adults (N100m). The temporal evolution of these three sources in children is different between hemispheres. In the children's left hemisphere, the P100m, N100m, and N250m sources are activated in a sequence, but in the right hemisphere the transient N100m appears stronger than the transient P100m source and its timing overlaps with that of the P100m source activation.

3.3 | Strength and timing of activation in adults

A 4 (time-windows) $\times$ 2 (hemispheres) $\times$ 2 (sites of stimulation) repeated-measures ANOVA was used to test the effect of ipsi versus contralateral presentation in the two hemispheres in adults in the different time-windows. The activation was generally stronger at 90–150 ms (N100m response) than in the other time-windows (main effect of time-window, $F(3,18) = 15.54$, $p < 0.001$; cf. Table 1). There was also a significant hemisphere $\times$ time-window interaction ($F(3,18) = 5.31$, $p < 0.01$), and the effect of hemisphere approached significance ($F(3,6) = 4.73$, $p = 0.07$, n.s.). Separate ANOVAs for each

time-window (with hemisphere and site of stimulation as within-subject factors) showed no significant effects prior to the N100m response. The N100m response was stronger in the right than left hemisphere (main effect of hemisphere, $F(1,9) = 5.7$, $p < 0.05$)) (Figure 5a). Activation at 150–400 ms (N2m) was also significantly stronger in the right than left hemisphere (main effect of hemisphere, $F(1,9) = 10.2$, $p < 0.05$).

The site of stimulation influenced activation strength only in the N100m time-window. The right-hemisphere N100m response was stronger to stimuli delivered to the contralateral left ear than ipsilateral right ear (ear-by-hemisphere interaction $F(1,9) = 7.7$, $p < 0,05$, effect of ear in the right hemisphere $F(1,9) = 39.4$, $p < 0.001$; Figure 5a). In the left hemisphere, the contralateral and ipsilateral activation strengths did not significantly differ ($F(1,9) = 2.3$, $p = 0.17$, n.s.), but the contralateral response reached the maximum earlier than the ipsilateral response ($F(1,9) = 9.9$, p < 0.05; cf. Table 2).

3.4 | Strength and timing of activation in children

A repeated-measures ANOVA with two time-windows $\times$ two hemispheres $\times$ two sites of stimulation was used to test the differences between the hemispheres and/or between sites of stimulation in the most consistent sources in child subjects, the P100m and N250m. The N100m sources were tested separately, as only in the right hemisphere there were enough subjects showing this source type to conduct statistical analysis. A significant main effect of time-window reflected stronger and longer-lasting activation in the later (>200 ms) time-window (N250m; mean amplitude $F(1,8) = 18.74$, $p < 0.01$; duration $F(1,8) = 29.9$, $p < 0.01$; cf. Table 1). There was also a significant main effect of hemisphere (maximum amplitude $F(1,8) = 6.1$, $p < 0.05$) and hemisphere-by-time-window interaction ($F(1,8) = 28.8$, $p < 0.01$). In a separate ANOVA for each time-window (with hemisphere and site of stimulation as within-subject factors) the N250m response was stronger in the right than left hemisphere (main effect of hemisphere, $F(1,8) = 31.0$, $p < 0.001$; Figure 5c). In the early time-window (P100m) there was a tendency towards the opposite pattern, with stronger activation in the left than right hemisphere ($F(1,11) = 3.2$ $p = 0.1$, n.s.).
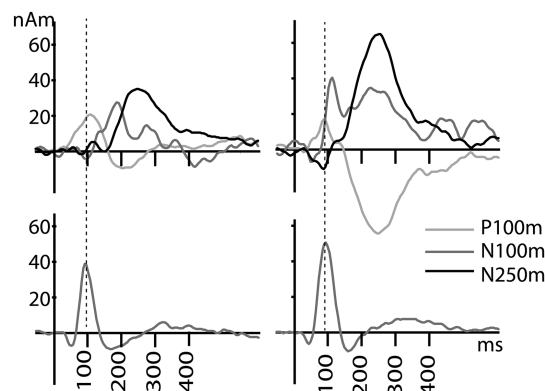

FIGURE 4 Mean time-course of activation. The amplitude as a function of time is given separately for the three response types: early activation reflecting upward current (light gray lines), early activation reflecting downward current (dark gray lines), and late activation reflecting downward current (black lines). Responses in children (upper row) and adults (lower row) are given separately

TABLE 1 Mean (SD) amplitude of the P100m (children)/P50m (adults), N100m, and N250 (children)/N2 (adults) responses in both age groups

		P100m/P50m		N100m		N250m/N2m	
		Left	Right	Left	Right	Left	Right
Children	LE	27 ± 14	26 ± 13	34 ± 9	46 ± 22	41 ± 21	73 ± 37
	RE	33 ± 18	24 ± 14	30 ± 18	34 ± 23	46 ± 2,555	62 ± 29
Adults	LE	9 ± 4	8 ± 4	33 ± 11	55 ± 16	10 ± 6	16 ± 8
	RE	9 ± 6	6 ± 4	40 ± 15	45 ± 23	11 ± 7	18 ± 11

In children, the early (<200 ms) transient responses to stimuli delivered to the contralateral ear were stronger than to stimuli delivered to the ipsilateral ear in both hemispheres but the effect was significant in different response types: In the left hemisphere, but not in the right, the P100m sources showed contralateral preference (hemisphere-by-ear interaction $F(1,11)$ = 4.4, p = 0.06, n.s.; effect of ear in left F (18,1) = 9.0, p < 0.01; effect of ear in right $F(18,1)$ = 1.0, p = 0.35, n.s.; Figure 5b). In the right hemisphere, the N100m sources were stronger ($F(7,1)$ = 8.4, p < 0.05) and earlier ($F(7,1)$ = 11.0, p < 0.05) to tones delivered to the contralateral left ear than ipsilateral right ear (Figure 5b). Note that for the N100m source, statistical tests could only be performed on the right-hemisphere responses due to the small number of subjects showing this response in the left hemisphere.

When the analysis was conducted on activation at ~100 ms regardless of the source type (i.e., N100m and P100m included in the same ANOVA), and thus all children were included at once, the activation was significantly stronger to contralateral than ipsilateral sounds in both hemispheres (effect of ear in the left hemisphere $F(18,1)$ = 6.3, p < 0.05; effect of ear in the right hemisphere $F(18,1)$ = 4.5, p < 0.05). Latency differed only in the right hemisphere (earlier responses to contralateral sounds, $F(18,1)$ = 10.9, p < 0.01) (cf. Table 2). In the late time-window (N250m), contralateral responses were stronger and earlier only in the right hemisphere (hemisphere-by-ear interaction, F (1,14) = 13.0, p < 0.01; effect of ear in the left hemisphere (F (15,1) = 2.4, p = 0.2, n.s.; effect of ear in the right hemisphere F (17,1) = 7.0, p < 0.05; Figure 5c).

3.5 | Correlation with neural measures and age

Although the age of children varied only within 8 months, age was significantly correlated with the strength of the long-lasting N250m

activation. The activation strength in the left hemisphere, but not in the right, decreased with age similarly for contra- and ipsilateral sounds (r = −0.72, p < 0.01 for age versus left-hemisphere response to left-ear sound, r = −0.70, p < 0.01 for age versus left-hemisphere response to right-ear sound). Activation in other time-windows was not significantly correlated with age.

3.6 | Adults versus children

The difference between groups was tested using independent samples t-test (Bonferroni corrected for multiple comparisons). The first phase of activation reflected an upwards/superiorly directed neural current both in adults (P50m) and in children (P100m) but occurred significantly later in children than in adults, in both hemispheres and for both ipsi- and contralateral sounds (left hemisphere, left ear $t(25)$ = 7.5, p < 0.001; left hemisphere, right ear $t(26)$ = 9.6, p < 0.001; right hemisphere, left ear $t(13)$ = 5.2, p < 0.001; right hemisphere, right ear $t(18)$ = 4.6, p < 0.001). This response was significantly stronger in children than in adults in both hemispheres (left hemisphere, left ear $t(23)$ = 5.0, p < 0.001; left hemisphere, right ear $t(25)$ = 5.3, p < 0.001; right hemisphere, left ear $t(15)$ = 4.4, p = 0.001; right hemisphere, right ear $t(13)$ = 4.4, p = 0.001). However, the first downwards/inferiorly directed neural current (N100m in adults and children) did not differ significantly between the age groups either in activation strength or in latency (for latency the difference approached significance: left hemisphere, left ear $t(12)$ = 9.7, p = 0.007, n.s.; left hemisphere, right ear $t(12)$ = 12.6, p = 0.003, n.s.; right hemisphere, left ear $t(17)$ = 7.9, p = 0.009, n.s.; right hemisphere, right ear $t(17)$ = 4.2, p = 0.003, n.s.). Note that in children the number of subjects showing this response type in the left hemisphere is small (n = 4).
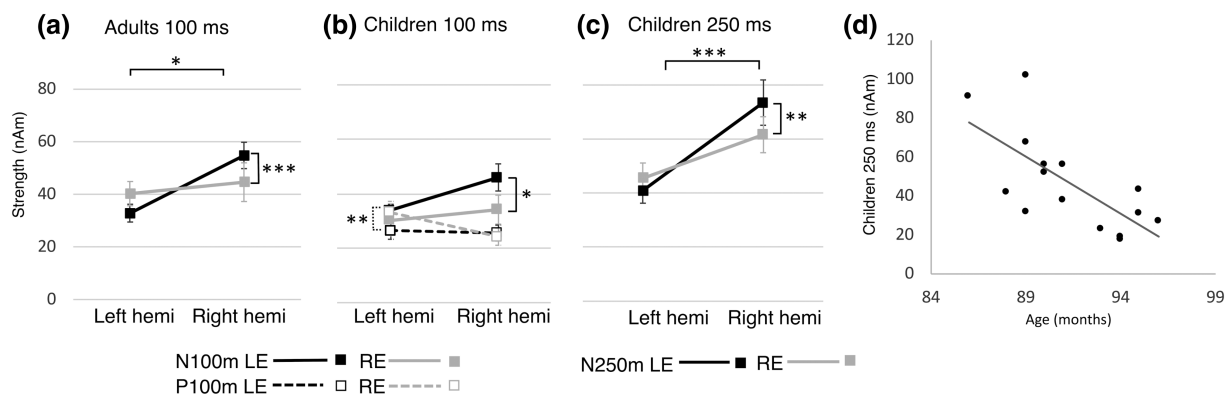

FIGURE 5 The peak amplitudes (mean +/− SEM) to the left and right ear sounds in the left and right hemisphere at 100 ms in adults (N100m) (a) and children (P100m and N100m) (b) and at 250 ms in children (N250m) (c). The statistically significant differences are depicted. The correlation between strength of activation at 250 ms (N250m) and age (months) (d) in children

TABLE 2 Mean (SD) latency of the P100m/P50m, N100m, and N250m/N2m responses in children and adults

		P100m/P50m hemisphere/		N100m		N250m/N2m	
		Left	Right	Left	Right	Left	Right
Children	LE	105 ± 300	97 ± 36	168 ± 24	122 ± 31	248 ± 32	239 ± 26
	RE	107 ± 18	105 ± 32	164 ± 19	139 ± 33	239 ± 205	253 ± 19
Adults	LE	49 ± 10	42 ± 9	92 ± 6	87 ± 9	324 ± 50	296 ± 70
	RE	46 ± 8	51 ± 11	85 ± 6	93 ± 9	298 ± 69	293 ± 69

For the later time-window (N250m in children and N2m in adults), children showed again a significantly stronger response than adults (left/right hemisphere, left/right ear: $t(19)$ = 5.6, p < 0.001; $t(19)$ = 5.3, p < 0.001; $t(20)$ = 6.4; p < 0.001, $t(24)$ = 5.8, p < 0.001). In children, the N250m response tended to emerge earlier than the weak N2 response in adults, but the difference only approached significance (left/right hemisphere, left/right ear: $(t(24)$ = −4.7, p < 0.001; $t(10)$ = −2.7, p = 0.024, n.s.; $t(10)$ = −2.4, p = 0.03, n.s.; $t(10)$ = −1.8, p = 0.1, n.s.).

4 | DISCUSSION

We used simple sine-wave tones to explore the electrophysiological response properties of the left and right auditory cortices in children. We clarified, first, whether the immature auditory system shows a similar preference to contralateral auditory input as is seen in the mature system, and second, whether there are functional differences in basic response properties between hemispheres in the auditory cortex in children. The obligatory responses in 7–8-year old children appeared clearly delayed and extended in time in comparison to those in adults. However, similarly to adults (Mäkelä et al., 1994), responses to the sounds from the opposite (contralateral) ear were stronger than those to the sounds from the ipsilateral ear. The contralateral preference appeared at 100 ms in both age-groups, regardless of the response type, and was thus linked with timing of neural processing rather than specific component structure. When the underlying source configuration was compared between age groups, the right hemisphere of children showed a more mature pattern of activation than the left hemisphere.

The major activation peaks in the evoked response waveform appeared in two time-windows: early (0–200 ms) and late (200–800 ms). In adults, the activation was mostly limited to the early time-window (N100m response) whereas in children the most prominent activation occurred in the later time-window (N250m). Children also showed early transient activation, but it was less systematic across individuals. This pattern is in line with earlier reports on development of AEP morphology (Albrecht, Suchodoletz, & Uwer, 2000; Ceponiene, Torki, Alku, Koyama, & Townsend, 2008; Johnstone et al., 1996). The "immature P50," typically detected at ∼100 ms in children (Albrecht et al., 2000; Sharma, Kraus, McGee, & Nicol, 1997; Wunderlich & Cone-Wesson, 2006) is followed (less consistently) by the N100/N100m response with latencies varying from 100 to 150 ms (Ceponiene, Rinne, & Naatanen, 2002; Cunningham et al., 2000; Kraus et al., 1993). These timings match with the latencies of the early peaks in the present study but, unlike in earlier reports, we demonstrate

individual-level variation in the appearance of the different response types (P100m and N100m, corresponding to the EEG responses P50 and N100), likely reflecting neurophysiological maturation. A similar change in emphasis to earlier and more transient activation by age has been reported also for the somatosensory modality (Pihko, Nevalainen, Stephen, Okada, & Lauronen, 2009). Indeed, the emergence of transient response components can be viewed as a measure of maturity of the auditory system. Although the emergence of the transient response, as such, has not been linked with behavioral skills, shortening of the activation in the later time-window (>200 ms) is correlated with enhanced reading speed (Parviainen et al., 2011), and increased amplitude in this later time-window has been observed in children with risk for reading disability (Hämäläinen et al., 2013).

The preference to contralateral stimulation was salient in both children and adults, and in both the left and right hemisphere. In adults, the prominent N100m was stronger and earlier to contralateral than ipsilateral sounds, in line with earlier findings (Mäkelä et al., 1993; Salmelin et al., 1999). Also in children, the activation in the early time-window (0–200 ms) showed a significant contralateral preference in both hemispheres, in line with earlier indications (Orekhova et al., 2013). From 200 ms onwards, the contralateral responses were significantly stronger only in the right hemisphere. Concordant with previous studies in adults, neither group showed contralateral effects prior to 100 ms (P30, P50; Mäkelä et al., 1994; McEvoy, Makela, Hamalainen, & Hari, 1994). In in-vivo electrophysiological recordings of rodents, the contralateral preference has been shown to develop gradually during postnatal life as a proportionally larger increase in responses to contralateral than ipsilateral stimulation (Mrsic-Flogel, Versnel, & King, 2006). This development takes place at a fairly early age, which is in line with our present results on humans showing a contralateral preference with adult latencies in 7–8 years old children. In both children and adults, the contralateral preference seems to be more pronounced in the right hemisphere. Right-hemisphere auditory responses have been shown to be particularly tightly linked with genetic regulation (Renvall et al., 2012). Together, these results may allude to stronger experience-driven plasticity in the left than right auditory cortex.

Our results in adults demonstrate a rightward bias in the general level of activation at ∼100 ms that persisted through the subsequent weaker response. In children, the rightward lateralization emerged only in the prominent 250-ms response; the preceding early peak of activation showed no significant differences between hemispheres. Indeed, although the contralateral dominance in children appeared at adult latencies, both the source configuration and the general level of activation deviated greatly from the adult pattern: contralateral preference thus did not seem to be linked with a specific component or

source configuration across age groups. Even within children, across the hemispheres, it emerged in source waveforms reflecting opposite current direction (P100m vs. N100m/N250m). Thus, although the timing of the contralateral preference seems mature, the general response pattern remains clearly immature in 7- to 8-year-old children, in passive auditory perception.

Intriguingly, the present data suggests maturational differences between hemispheres in children, reflected as different source configurations. Although the details of the cortical generators cannot be reached even with advanced noninvasive brain imaging methods, data analysis at the source level yields more reliably comparable measures between different age groups than working only on the sensor level. ECDs have an advantage of providing the direction of the current flow in the estimate, in addition to amplitude and location (Hämäläinen et al., 1993). Interestingly, also anatomical MRI studies indicate asymmetrical development of the peri-sylvian areas, and significant age-related changes especially in the right hemisphere (Sowell et al., 2002).

Concordant with previous MEG findings, the prominent ∼100-ms activation in adults reflected an underlying neural current directed roughly from superior to inferior direction in the upper bank of Sylvian fissure, and it was preceded by a weak response with the opposite direction of current flow (cf. Mäkelä et al., 1994). Few earlier studies have used source modeling algorithms to clarify the characteristics of the neural currents generating the auditory evoked responses in infants (Huotilainen, 2008; Ortiz-Mantilla et al., 2012) and children (Orekhova et al., 2013; Paetau, Ahonen, Salonen, & Sams, 1995; Parviainen et al., 2011; Takeshita et al., 2002). Our present results are in line with those studies showing prominent long-lasting activation in children, often termed N250(m). Our results further demonstrate that this long-lasting activation pattern reflects current flow with comparable orientation and location to the adult N100m. This response is, however, not merely a delayed N100m, as the transient 100-ms response has been shown to emerge as an early separate deflection that precedes the N250/N2 response (Ceponiene et al., 2008). There seems to be a developmental shift in emphasis from longer-lasting sluggish auditory activation to early transient activation (Albrecht et al., 2000; Parviainen et al., 2011). Indeed, we found a significant reduction in the amplitude of the N250m response by age even with only 8 months of variability in birth dates. We found no significant changes in its latency, suggesting the N250m indeed reflects a specific, gradually vanishing process in the underlying circuitry.

Conventionally, age-related changes are studied by comparing the activation at the group level, and/or only amplitude and latency measures are collected. Consequently, the possible individual differences in source orientation have not been approached earlier. As regards the early time-window of our study (0–200 ms), previous reports have shown either superiorly oriented (comparable to P50; e.g., Albrecht et al., 2000; Ponton et al., 2002) or inferiorly oriented (comparable to N100; e.g., Takeshita et al., 2002) directions of modeled current; the analysis has been conducted without reference to current direction (Kotecha et al., 2009); or the analysis has been based on squared power where any information on current directions is lost. Our study indicated marked difference in the source configuration in children in the early time-window, with P100m, N100m, or both

source types present. A similar overlap of different response types in children was recently reported by Orekhova et al. (2013). Due to a wide age-range in their study, individual differences (vs. age-related change) could not be approached, and the stimulus material (3.4 ms white noise clicks) was markedly different from the present study. However, both studies demonstrate larger diversity of responses in children than in adults, in the early time-window. Given that adults show a systematic and stable P50-N100 sequence of responses (Mäkelä et al., 1994), the present result indicates a remarkable interindividual variability in basic response properties in the maturing brain and highlights the importance of individual-level analysis.

Notably, the appearance of the two response types (P100m, N100m) was not symmetric across the hemispheres. The left hemisphere was dominated by the "immature" P100m sources but, in the right hemisphere, half of the children showed an N100m source, comparable to the N100m sources in adults. As N100m activation is generally shown to emerge developmentally later than P50m (Ponton et al., 2002), our result speaks to a more mature pattern of activation in the right than left hemisphere. Faster maturation of the right hemisphere would be in agreement with earlier findings by Kotecha et al. (2009) who reported faster shortening of AEF component latencies in the right than left hemisphere. Further studies are needed to establish whether such maturational lag in the left-hemisphere auditory cortex is limited to the studied age range, or reflects a more general pattern. Some indication of rightward maturation of temporal areas has been shown in anatomical studies, where gyrification and formation of sulci during fetal development takes place 2 weeks earlier in the right than left hemisphere (Chi, Dooling, & Gilles, 1977; Dubois et al., 2008).

A comparison between the structural properties and functional (BOLD) responses in children, adolescents and adults indicated larger interindividual variance in adolescents and adults than in children in some of the (right hemisphere) perisylvian areas, but smaller variance in other (left hemisphere) areas (Bonte et al., 2013). While it initially looks like our results indicate the opposite, that is, less interindividual variance in timing of activation in adults, these results rather emphasize the importance of integrating information from structural, BOLD and electrophysiological measures to better understand the developmental changes in the brain. It is likely that the timing of neural activation, especially in the early sensory cortices, shows a decrease in interindividual variability and reflects the general requirements posed by shared (auditory) communication signals. However, the structural properties as well as later and slower response properties (captured by BOLD response) could well reflect more unique effects of auditory experience, as speculated earlier (Bonte et al., 2013; Dehaene-Lambertz et al., 2010).

As compared with adults, the auditory activation in children thus appears to show a stronger emphasis to later, long-lasting activation and a more variable pattern of the direction of neural current flow underlying the early transient activation. Although N2/N250 components have been repeatedly reported in infants and children, surprisingly little is known about their role in development. As this prominent response is evoked even by passive stimulation with pure tones, it seems not to be associated with cognitive processing but reflects part of the automatic chain of circuit level processes in children. In earlier studies, a similar prolonged response has been

demonstrated for other sound types (speech) (Parviainen et al., 2011) and in variable attentional conditions (Takeshita et al., 2002), indicating that this pattern is rather general in nature and may be associated with developmentally specific processes in the brain (cf. Albrecht et al., 2000; Takeshita et al., 2002). Furthermore, N250m in children seems to differ from the activation around 200 ms in adults (N2m), which is typically related to active attentional processing and is absent especially in magnetic evoked fields during passive stimulation (Parviainen et al., 2006). Indeed, in the present study, passive presentation of simple tones did not evoke activation beyond the P50m-N100m complex in adults. Further research is needed to clarify the role of activation within this time-window in developing versus mature brain.

The shift from sluggish to more transient, fast responses has been interpreted as increased automatization across development (Albrecht et al., 2000). Based on post-mortem studies and studies of nonhuman species, postnatal development is accompanied by continued changes in myelination and synaptic strength. At the neuronal circuit level, the inhibitory processes are suggested to mature later than excitatory processes (Wehr and Zador, 2003), and the maturation of this balance is associated with narrowing of synaptic integration window and increasing temporal acuity (Oswald and Reyes, 2010). Although the link from in-vivo recordings in rodents to human electrophysiological measures is yet to be established, it would be tempting to associate these findings as potential underlying mechanisms for the changes seen in data on human children, that is, the observed shift in emphasis from the N250m to the N100m response.

To conclude, the basic response properties of auditory cortex, studied using passive presentation of sounds, remain clearly immature at 7–8 years of age, and reflect a maturational difference between hemispheres with more adult-like response type in the right hemisphere. However, the sensitivity to contralateral versus ipsilateral input seems to occur at the same latencies as in the adult cortex.

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